Mini-Review

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Autoimmune hepatitis following COVID-19 vaccination: Clinical characteristics of 35 reported cases

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SUMMARY The coronavirus disease 2019 (COVID-19) vaccines have been shown to be effective in protecting people from severe disease progression, hospitalisation and death. However, a wide range of side effects have been reported worldwide. New onset or flare-up of autoimmune hepatitis (AIH) is an extremely rare adverse event following COVID-19 vaccination, with the majority of cases presenting with mild symptoms. Unfortunately, there have been cases of fatal complications. In this mini-review, we have summarised the clinical characteristics of a total of 35 currently reported cases of AIH after COVID-19 vaccination and suggest that patients with autoimmune diseases may be at higher risk of developing AIH after vaccination.

Keywords COVID-19, vaccines, adverse events, autoimmune hepatitis

Coronavirus disease 2019 (COVID-19) vaccines are becoming an important means of reducing the likelihood of severe progression and death from infection, and may also act as a risk factor for the induction of autoimmune phenomena. Recently, there have been increasing reports of autoimmune disease flares or new onset after COVID-19 vaccination, ranging from mild to life-threatening. It is therefore necessary to develop effective strategies to identify and manage these adverse events in routine clinical practice. With more than 60% of the world's population having received at least one dose of the vaccine, there is an opportunity to further investigate the rare adverse events, particularly those not reported in the original trials.

Autoimmune hepatitis (AIH) after COVID-19 vaccination was first reported by Bril *et al.* (*1*). To the best of our knowledge, a total of 35 cases of AIH following COVID-19 vaccination have been reported worldwide, including two deaths (Table 1) (*1-26*). AIH after COVID-19 vaccination has been observed with mRNA vaccines (mRNA-1273; BNT162b2), recombinant adenovirus vaccines (ChAdOx1; Covishield) and inactivated vaccines (CoronaVac; Sinopharm). Patients range in age from 35 to 89 years with a female predominance (80%) and no cases have been reported in children or adolescents. Jaundice, pruritus, choluria and asthenia are the most common manifestations at onset, except in three cases which were asymptomatic and only hypertransaminasemia was found on routine liver function tests (*9,10,17*). Of these three cases, two developed obvious symptoms after a latency period of 5 weeks, while the other remained asymptomatic and liver enzymes returned to normal levels after steroid therapy (*9*).

The majority of cases occurred 1-3 weeks after the first dose of COVID-19 vaccine, but several cases showed rapid onset at 2-3 days, while one late case occurred 51 days after vaccination. Five cases showed significant symptoms 2 days to 3 weeks after the second dose of vaccine, and one case of AIH flare-up occurred after the third dose of vaccine (*26*). Usually, symptoms after the first dose were mild or non-specific and became more obvious or worse with the second dose. In general, physical and imaging examinations showed no obvious positive findings, except for occasional hepatomegaly. Levels of total/direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), alkaline phosphatase (ALP) and international normalised ratio (INR) were elevated in the early phase of the disease in most cases, and no hepatophilic virus tests were positive, except in one case with a history of HCV treatment (*24*).

Anti-nuclear antibodies (ANA) were positive in the majority of AIH cases, mainly with a haemorrhagic or speckled pattern. The second most common autoantibody was anti-smooth muscle antibody (ASMA). Four cases were negative for autoantibodies (*2,4,5,18*). Total IgG was often elevated in most cases. Although the efficacy of these COVID-19 vaccines has not been fully reported, two cases had an extremely

Table 1. 35 cases of autoimmune hepatitis reported after COVID-19 vaccination

Study	Vaccine	Gender	Age (year)	Commodity, medical history	Time to onset	Antibody	Liver histology	Steroid response
Bril, *et al.* (*1*)	BNT162b2	Female	35	Post-partum, Hypertension	1 week post vaccination	ANA+homo Anti-dsDNA+	AIH, eosinophils score (Rev)=18	Response
Rela, *et al.* (*2*)	Covishield	Female	38	Hypothyroidism	20 days post vaccination	ANA+	AIH, eosinophils score (Simp)=6 score (Rev)=15	Response
Rela, *et al.* (*2*)	Covishield	Male	62	Diabetes, jaundice history	16 days post vaccination	Anti-HBV core+ ANA-,ANCA-, SMA-, LKM-1-	AIH, fibrosis (Ishak stage 2/6)	No,dead
Erard, *et al.* (*3*)	BNT162b2	Female	80	None	10 days post vaccination	ANA+	AIH	Response
Erard, *et al.* (*3*)	mRNA-1273	Female	73	None	21 days after vaccination	ANA+	AIH	Response
Erard, *et al.* (*3*)	ChAdOx1	Female	68	None	20 days after vaccination	ANA+	AIH	No, dead
Fimiano, *et al.* (*4*)	BNT162b2	Female	63	Hypothyroidism, familial autoimmunity	51 days post vaccination	ANA-,AMA-, LKM-1-,ANCA- Anti-SARS-CoV2 spike (high)	AIH	Response
Camacho-Domínguez, *et al.* (*5*)	ChAdOx1	Male	79	None	14 days after 1st dose, 15 days after 2nd dose exacerbation	ANA+gran, ASMA+ Anti-SARS-CoV2 spike (high)	AIH, ductular reaction, eosinophils	Response
Ghielmetti, *et al.* (*6*)	mRNA1273	Male	63	Diabetes, ischemic heart disease	1 week post vaccination	ANA+spec APCA+	AIH	Response
Vuille-Lessard,*et al.* (*7*)	mRNA1273	Female	76	Hashimoto, SARS-CoV-2, urothelial cancer	2-3 days after 1st dose	ANA+homo ASMA+, AAA+, ANCA+	AIH, score (Simp)=8	Response
Suzuki, *et al.* (*8*)	BNT162b2	Female	80	Gastroesophageal reflux disease	10 days after 2nd dose	ANA+Cent	AIH	Response
Suzuki, *et al.* (*8*)	BNT162b2	Female	75	Dyslipidemia	4 days after 2nd dose	ANA+spec/homo ANA+	AIH	Response
Suzuki, *et al.* (*8*)	BNT162b2	Female	78	Primary sclerosing cholangitis	7 days post vaccination	ANA+	AIH, eosinophils	Response
Palla, *et al.* (*9*)	BNT162b2	Female	40	Sarcoidosis	1 month post vaccination (asymptomatic)	ANA+	AIH, fibrosis	Response
Garrido, *et al.* (*10*)	mRNA1273	Female	65	Polycythemia vera (JAK2 V617F)	2 weeks post vaccination (asymptomatic), 5 weeks symptomatic	ANA+Spec	AIH	Response
Avci, *et al.* (*11*)	BNT162b2	Female	61	Hashimoto, SARS-CoV-2, hypertension	2 weeks post vaccination	ANA+ ASMA+	AIH, fibrosis	Response
Cao, *et al.* (*12*)	CoronaVac	Female	57	None	2 weeks post 1st vaccination exacerbation after 2 days post 2nd dose	ANA+hom ASS-A+ ACENP-B+ ASS-B+	AIH, fibrosis	Response
Lodato, *et al.* (*13*)	BNT162b1	Female	43	Dyslipidaemia with ALT increase	15 days post 1st vaccination, exacerbation after 2 days post 2nd dose	ANA-,ASMA-, LKM-1-,AMA-, ENA-	AIH, biliary injury and eosinophils	Response
Zhou, *et al.* (*14*)	mRNA-1273	Female	36	Primary sclerosing cholangitis	11 days post 1st vaccination, return of symptoms after 2nd dose	ANA+hom Anti-dsDNA+	AIH, ductular reaction, eosinophils	Response
Zin, *et al.* (*15*)	mRNA-1273	Male	47	None	3 days post vaccination	ANA+	AIH, fibrosis, eosinophils	Response
Rocco, *et al.* (*16*)		Female	80	Hashimoto, Glomerulonephritis	1 week after completing schedule	ANA+spec	AIH, Score (Rev)=19	Response
Clayton-Chubb,*et al.* (*17*)	BNT162b2	Male	36	Hypertension	26 days post vaccination (asymptomatic), 34 days symptomatic	ANA+	AIH, score (Rev)=15	Response

Notes: Antinuclear antibody (ANA) (hemo=hemogeneous pattern; spec=speckled pattern), anti-smooth muscle antibody (ASMA), Antimitochondrial antibodies (AMA), Anti-Extractable Nuclear Antigen (ENA), Anti-Sjögren syndrome antigen A (ASS-A), Anti-major centromere autoantigen B (ACENP-B), Anti-liver-kidney microsome-1(LMK-1), anti- soluble liver antigen/liver-pancreas (ASLA/LP).

Table 1. 35 cases of autoimmune hepatitis reported after COVID-19 vaccination (continued)

Study	Vaccine	Gender	Age (year)	Commodity, medical history	Time to onset	Antibody	Liver histology	Steroid response
McShane, *et al.* (*18*)	mRNA1273	Female	71	Cholecystectomy, hip replacement	4 days post vaccination	ASMA+	AIH, eosinophils	Response
Tan, *et al.* (*19*)	mRNA1273	Female	56		5 weeks post vaccination	ANA+, ASMA+	AIH, eosinophils, fibrosis	Response
Ghorbani, *et al.* (*20*)	Sinopharm	Male	62	None	3 days after 2nd dose	ANA-, ASMA-, LKM-1-	AIH, grading, staging Ishak modified HAI, 11/18, 1/6	Not use
Londoño,*et al.* (*21*)	mRNA1273	Female	41	Premature ovarian failure	no liver specific after 1st dose, significant after 1 week post 2nd dose	ANA+, ASMA+, SLA+, LC1+	AIH, fibrosis score (Simp)=8	Response
Mekritthikrai, *et al.* (*22*)	CoronaVac	Female	52	None	1 week after 2nd dose	ANA+Spec, ASMA+	AIH, fibrosis	Response
Izagirre, *et al.* (*23*)	ChAdOx1	Female	47	Hypothyroidism	24 days after 1nd dose	ANA+	AIH,score (Simp)=8	Response
Izagirre, *et al.* (*23*)	BioNTech	Male	72	Ischemic heart disease	46 days after 2nd dose	ANA+hom	AIH,score (Simp)=7 Eosinophils	Response
Izagirre, *et al.* (*23*)	ChAdOx1	Female	62	Celiac disease	4 days after 2nd dose	ANA+, ENA	AIH, score (Simp)=8 eosinophils	Response
Izagirre, *et al.* (*23*)	BioNTech	Female	72	None	14 days after 2nd dose	ANA+hom	AIH, score (Simp)=8	Response
Izagirre, *et al.* (*23*)	BioNTech	Female	59	Hypothyroidism	9 days after 1nd dose	ANA+Spec	None	Response
Hasegawa, *et al.* (*24*)	BioNTech	Female	82	HCV	4 day after 1nd dose	ANA+	AIH	Response
Brubaker, *et al.* (*25*)	BioNTech	Female	35	AIH, chronic sinusitis, insomnia	2 weeks after 2nd dose	ASMA+	AIH (onset)	Response
Mahalingham, *et al.* (*26*)	BioNTech	Female	32	AIH, liver transplantation	3 weeks after 3nd dose	ASLA/LP+	AIH	Response

Notes: Antinuclear antibody (ANA) (hemo=hemogeneous pattern; spec=speckled pattern), anti-smooth muscle antibody (ASMA), Antimitochondrial antibodies (AMA), Anti-Extractable Nuclear Antigen (ENA), Anti-Sjögren syndrome antigen A (ASS-A), Anti-major centromere autoantigen B (ACENP-B), Anti-liver-kidney microsome-1(LMK-1), anti- soluble liver antigen/liver-pancreas (ASLA/LP).

high vaccine antibody titre of 1,000 fold the upper normal level (*4,5*).

Histology of liver biopsies revealed typical AIH characterised by interface hepatitis, lymphoplasmacytic infiltrate and varying degrees of hepatocyte necrosis from scattered to widespread. Ten cases were classified as definite AIH according to simplified or revised systems. Eosinophilic infiltrate was found in 8 cases, and 4 cases showed ductal reaction, characterised by proliferation of reactive bile ducts induced by liver injury. In addition, significant hepatic fibrosis was observed in one fifth of the cases, suggesting the possibility of pre-existing subclinical liver disease in some patients.

Most patients with AIH had a good response to steroid treatment and no relapses were reported after drug-withdrawal. Two cases with poor steroid response died of liver failure (*2,3*). The deceased patients were not receiving concomitant life-threatening medications prior to COVID-19 vaccination. There was also no significant difference in the onset of clinical manifestations between the deceased and cured cases, except that one deceased case had two episodes of jaundice in the past decades (*2*).

There appears to be an association between the occurrence of AIH and the patients' pre-existing autoimmunity. At least 7 cases had an autoimmune disorder prior to COVID-19 vaccination, including Hashimoto's thyroiditis (3 cases) (*7,11,16*), primary sclerosing cholangitis (2 cases) (*8,14*), glomerulonephritis (1 case) (*16*), sarcoidosis (1 case) (*9*), and celiac disease (1 case) (*2,3*). Two patients with AIH had a history of symptomatic COVID-19 infection (*7,11*), both in the context of Hashimoto's thyroiditis.

More recently, Brubaker *et al*. (*25*) described a 35-year-old female AIH patient in remission who had a relapse two weeks after the second dose of mRNA vaccination. Mahalingham *et al.* (*26*) reported a stable post-transplant AIH patient who had a flare coinciding with mRNA vaccination. Therefore, COVID-19 vaccination may not only trigger the onset of AIH, but also promote immune reactivation. Although objective causality has not yet been established, the time course from vaccination to altered liver manifestations was significant in almost all reported cases. A significant percentage of patients had a history of liver-damaging drugs, suggesting that AIH following COVID-19 vaccination may be drug-induced rather than vaccine-induced. Liver histology in some cases also showed a marked eosinophilic infiltrate, characteristic of drug-induced autoimmune hepatitis (DIAIH). However, there are two lines of evidence against this possibility: firstly, DIAIH usually has a latency period of 2 to 24 weeks after drug treatment, and secondly, no recurrence has been observed after withdrawal of glucocorticoids in all reported cases. Therefore, it is now widely accepted that vaccines, which stimulate an abnormal immune response, are the main cause of AIH. Another important piece of evidence is that antibodies against the spike protein S1 of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had a high affinity for human liver proteins such as transglutaminase (*27*), suggesting that vaccination may directly induce spike-directed antibodies and thus autoimmune hepatocyte damage in predisposed individuals.

Although the underlying mechanisms have not been elucidated, various hypotheses have been suggested to establish a relationship between clinical manifestations of AIH and the active ingredients and adjuvants of vaccines (*28*). One of the major explanations for AIH following COVID-19 vaccines, particularly inactivated ones, is molecular mimicry, which is based on significant homology between amino acid sequences of vaccine determinants and prominent liver antigens (*22*). Moreover, the incorporation of lipid nanoparticle and adenovirus vectors in recently authorized vaccines could potentially enhance the inflammatory background, consequently resulting in an amplified immune response. Recent studies have also suggested that various types of vaccines may facilitate the promotion of autoimmunity through different mechanisms. mRNA vaccines may bind to pattern recognition receptors (PRRs) like Toll-like receptor 7 (TLR7), initiating multiple pro-inflammatory cascades, while adenovirus vaccines may activate innate immune responses by involving TLR9 to produce type 1 interferon secretion (*29*).

Another special group that requires our attention are vaccinated children. Clinical manifestations of AIH in children can be very variable, ranging from acute to chronic or even silent presentations (*30*). Although AIH after COVID-19 vaccination has not been reported in children and adolescents, several subclinical cases with hypertransaminasemia have been reported, suggesting that AIH may be a potential complication of vaccination in this population. Therefore, it is important to monitor vaccinated children for signs and symptoms of AIH, as it is possible that the cases identified now are just the tip of the iceberg, and as the vaccinated population expands to include children, asymptomatic or symptomatic paediatric AIH following COVID-19 vaccination may emerge in the near future. In children with abnormal liver function tests after COVID-19 vaccination, AIH should be considered and early diagnosis must be made to avoid progression to cirrhosis without treatment.

There is no doubt that vaccines have an important role to play in controlling the COVID-19 pandemic. As a large percentage of the world's population has been rapidly vaccinated, particularly with the introduction of mRNA vaccines in humans for the first time, in addition to the benefits of vaccination, some rare but serious adverse events are becoming more apparent. A number of autoimmune phenomena have been reported following COVID-19 vaccination, with different

clinical manifestations adding to the complexity of the existing human disease spectrum. As a life-threatening autoimmune adverse event, the risk assessment of AIH before and after COVID-19 vaccination should be of particular concern. Therefore, more efforts are needed to evaluate the predisposing autoimmune situation before and after COVID-19 vaccination. Furthermore, although a clear association between COVID-19 vaccination and AIH has been established, multicentre, prospective, longitudinal studies enrolling patients worldwide should be conducted in the future to clarify the clinical diversity, detailed pathological mechanisms, outcome prediction and management.

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